No.* 5573.149

379-389

THE TRUSTEES OF THE PVBLIC LIBRARY
OMNIVM LVX CIVIVM
OF THE CITY OF BOSTON
1852 1878

GIVEN BY

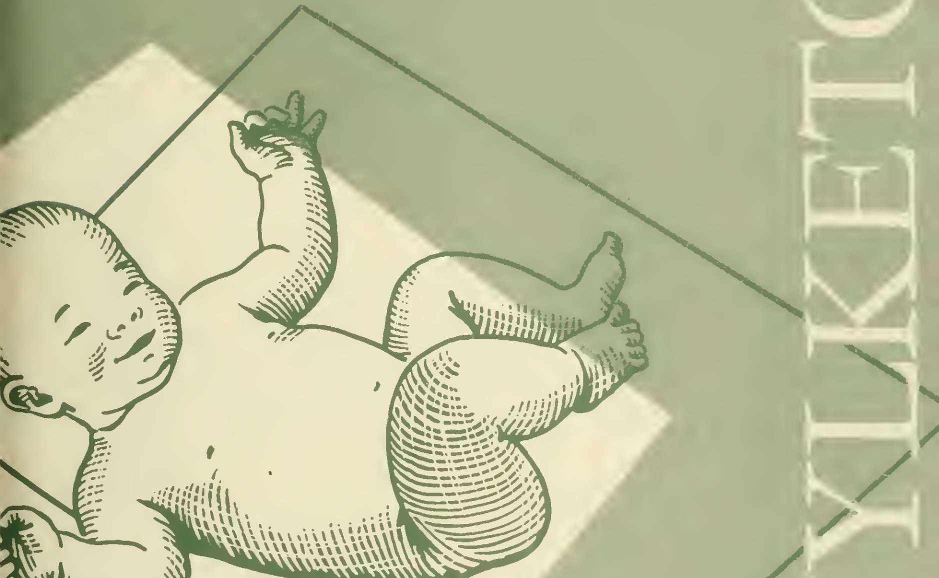
U. S. SUPT. OF DOCUMENTS

3

*5573.149

3F—

HENYLKETONURIA



PHENYLKETONURIA

The appearance of a dark blue green color—similar to the spot above—when ferric chloride is dropped in a sample of urine or onto a wet diaper suggests the presence of phenylpyruvic acid.

CHILDREN'S BUREAU PUBLICATION NO. 388 • 1961

an inherited metabolic disorder associated with mental retardation

PHENYLKETONURIA

WILLARD R. CENTERWALL, M.D.
SIEGRIED A. CENTERWALL, M.D.

Department of Pediatrics, College of Medical Evangelists,
School of Medicine, Los Angeles, California

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Social Security Administration • Children's Bureau • 1961

foreword

Boston Public Library
Superintendent of Documents

JUL 17 1961

DEPOSITORY

Great strides have been made in improving and safeguarding the health of mothers and children of this country. The risks of pregnancy have been considerably reduced. Many of the threats to the lives of newborn babies have been removed, and more infants survive than ever before.

Among those who survive, however, are some who are not fully equipped to grow and develop normally. At birth, some have defects which we have been unable to prevent.

Correction and prevention of these defects is one of the most challenging frontiers in medical research today.

This bulletin is a report of one such defect, phenylketonuria. While it affects only a small number of infants born each year, if untreated, the condition results in the tragic destruction of the mind of the child, although he may have been born with normal mental potential.

Hopefully, some of the approaches to screening, early detection, and treatment described here for phenylketonuria can be applied to similar conditions and thus furnish clues for dealing with other inherited defects.

The Bureau is proud to publish this work by Doctors Willard and Siegried Centerwall. Briefly, it introduces some methods of detecting and managing phenylketonuria, and is addressed to public health workers and physicians in general practice.

Katherine B. Oettinger

KATHERINE B. OETTINGER,
Chief, Children's Bureau.

table of contents

NCIDENCE AND GENETICS 2

BIOCHEMISTRY 4

CLINICAL COURSE 5

SCREENING PROGRAMS 6
  Mentally Retarded Populations 6
  Well Baby Populations 8
  Other High Risk Groups 9

TESTING METHODS 9
  The Test-Tube Test With Ferric Chloride 10
  The Diaper Test 11
  The Phenistix Test 12
  The Filter Paper Test 12
  The Dinitrophenylhydrazine Test-Tube Test 13
  Serum Phenylalanine Determination 14

DIETARY TREATMENT 15

SUMMARY 20

APPENDIX A 21

APPENDIX B 22

APPENDIX C 24

BIBLIOGRAPHY 25

PHENYLKETONURIA

PHENYLKETONURIA (PKU) holds a unique position in the field of mental deficiency. It is unique because it is easily detected and when diagnosed early the mental deficiency of this disorder can be prevented or favorably modified by special dietary management.[1,2]

The history of PKU dates back to the early 1930's to a family in Norway with two retarded children.[3] The mother was haunted by the notion that these children had a peculiar odor. Her efforts to get help for her children and to learn the cause of this odor led her from doctor to doctor over a period of years. Finally she interested a Norwegian physician and biochemist, Dr. Ashbörn Fölling.

In the process of examining the children, Dr. Fölling discovered that the urines of both reacted with ferric chloride to give an unusual green color. This he proved was due to the presence of phenylpyruvic acid, which he was able to crystallize in pure form from the urine samples. It is by the same simple ferric chloride urine test and modifications thereof [4,5,6] that early diagnosis of PKU is made possible today.

The substance which was responsible for the peculiar odor of the two children is one of the byproducts of phenylpyruvic acid in the urine, phenylacetic acid. Increased amounts also occur in the sweat of PKU patients, and it is possible to detect this odor in the hair or on the skin of such persons who have not bathed recently. The odor hardly fails to bring some association to the mind of the person who first smells it. It has been variously described as a musty, horsy, or barnlike odor.

A urine test survey of several hundred patients in two nearby institutions for the mentally retarded led to the discovery of eight additional patients with this disorder including two more sibling pairs. That same year Dr. Fölling's discoveries were published in the Norwegian [7] and German [8] medical literature. He postulated that the abnormality was an inherited error in the metabolism of phenylalanine, and he called it "imbecillitas phenylpyruvica."

INCIDENCE AND GENETICS

As news of this newly discovered disease spread, patients in institutions for the mentally retarded in many countries were similarly tested. Out of such studies came figures for incidence, determinations of type of inheritance, and a fairly complete clinical picture of the disease.[9] Study of these patients also provided information by which much of the metabolic error eventually was mapped out. Because phenylpyruvic acid, the substance responsible for the green color reaction with ferric chloride in the urine, is a phenylketone, the name phenylketonuria was suggested for this disease.[10] To date, this is the name of preference.

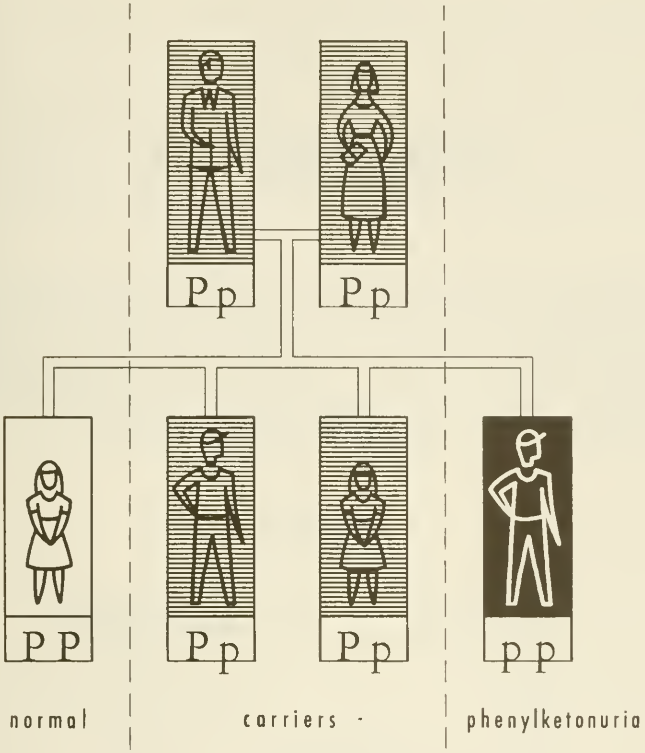
It was soon discovered that PKU is found on the average in one-half to 1 percent of institutionalized mental defectives. Interpolating from this prevalence, it has been estimated that PKU occurs once in every 20,000 to 40,000 live births.[9,11] Sexes are essentially equally affected and all races appear to be involved. However, the incidence is relatively higher in people of European stock [9] and is particularly low in people of Jewish [12,13] or Negro [14,15] ancestry.

Because PKU often involves more than one child in a family, from the beginning it was recognized as a familial disorder.[7,8] When it was determined that the parents were normal and that approximately one in four children in the involved families had PKU, it was concluded that PKU was inherited by a simple autosomal recessive gene.[9,10] The following diagram represents the mode of inheritance in a classical PKU family (fig. 1).

In this situation the normal parents are each carriers (Pp) of the defective gene for PKU. The children from two such parents can be noncarriers (PP) or carriers like the parents (Pp), or have two abnormal genes (pp) and have phenylketonuria (PKU). Thus, each pregnancy of such parents has a 1-in-4 chance of resulting in a PKU child (pp) and a 3-in-4 chance of resulting in a normal child (PP and Pp).

If we assume that the incidence of PKU in the general population is 1 in 20,000, then it can be determined that 1 in 70 of the general population is a carrier for this disease. This figure is derived by

Figure 1.—Inheritance Pattern for PKU.



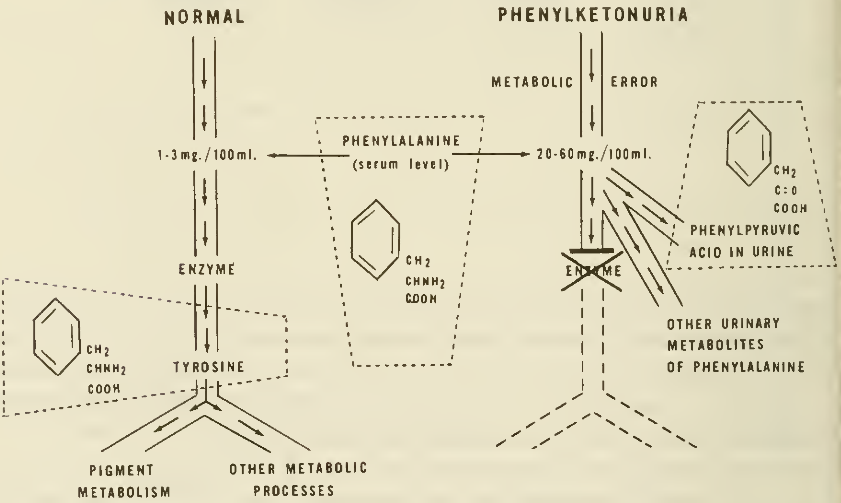
dividing 20,000 by 4 and then taking the square root. To test this figure one can calculate in reverse that the chance of two such carriers in the general population to marry each other would be 70×70 or once in 4,900 (or roughly 5,000) marriages. If each of these 5,000 couples, including the "carrier" couple, had four children, then one of the 20,000 offspring would be expected to have PKU.

It should be realized that exact incidence of PKU and thus the incidence of carriers is as yet unknown. This fact will not be determined until reports are gathered from wide-scale screening programs[4,5,6] of the general population and more extensive use is made of improved methods for "carrier" detection. At present each of several proposed means of determining "carriers," i.e., phenylalanine tolerance tests,[16] fasting serum phenylalanines,[17] and phenylalanine-tyrosine ration,[18] although useful, has some limitations in clinical application—mainly because of overlap between normal and "carrier" results.

BIOCHEMISTRY

Phenylketonuria is known as an inborn error of metabolism. The basic defect caused by the PKU gene is lack of the parahydroxylase enzyme which normally changes the essential amino acid phenylalanine to tyrosine.[19,20,21] The metabolic pathways affected by this enzyme deficiency are shown in the diagram (fig. 2).

Figure 2.



Because the mother has essentially normal metabolism, the baby is protected before birth. As soon as a newborn baby with PKU begins to take milk (breast milk or cow's milk), phenylalanine, which constitutes approximately 5 percent of all proteins, is absorbed.

Blocked in its normal metabolic pathway, the phenylalanine builds up to serum levels of about 20 times the normal.* This takes place fairly rapidly, so that by the time the infant is 1 [22] to 6 [1] weeks of age, the abnormal byproducts of this high serum phenylalanine begin to appear in the urine. It is believed that the continued high level of phenylalanine or its related metabolites is responsible directly or indirectly for the mental retardation. This view is supported by the fact that low phenylalanine diets started on PKU infants in the early months of life, (so that serum phenylalanine levels remain within the normal or near-normal range), has resulted in normal mental development.[1, 2]

Many questions remain yet unanswered about PKU metabolism. Why, for example, is there little or no correlation between the level of elevated serum phenylalanine and the degree of mental retardation? Why does a rare case of PKU now and then develop normally without any treatment? What role is played by the associated abnormality in tryptophane metabolism? [23]

CLINICAL COURSE

The untreated PKU patient is born apparently normal but begins to show retardation early in life. At about 3 to 4 months of age, a subtle change may be noticed. The infant begins to lose interest in his surroundings, and thereafter development is slowed down or arrested until by 2 or 3 years of age most are in the "below 50 I.Q." range of mental deficiency. (Of the known untreated cases in institutions, 90 percent fall into this bracket [9,24] (fig. 3).) Occasional untreated cases (perhaps 10 percent) are only mildly retarded and a few cases (less than one-half percent) have been reported with normal mentality.[2]

PKU children usually are fairly well-developed physically and have no truly diagnostic stigmata (other than the characteristic musty odor). There may be slight stunting of height and some have smaller than average head sizes.

The average age for sitting alone is from 12 to 15 months; the average age for walking is 2½ years, for talking 3½ years. Some never learn to walk; many never learn to talk. Approximately 80 percent are blonder than their parents and normal siblings. Behavior patterns are frequently autistic, hyperirritable, and destructive. About 80 percent have abnormal EEG's and approximately 25 percent have convulsions. (Convulsions are uncommon after 10 years of age.) The more severely involved cases may show signs of upper motor neuron damage such as positive Babinski and ankle clonus. About 25 percent of PKU patients have eczema, which is puritic and not limited to any specific areas of the body and which may have its onset within the first few months of life.[24]

---

*If a newborn PKU infant doesn't receive milk (proteins) the serum phenylalanine level still will show some rise within a few days due to catabolism of body proteins.

SCREENING PROGRAMS

Mentally retarded populations

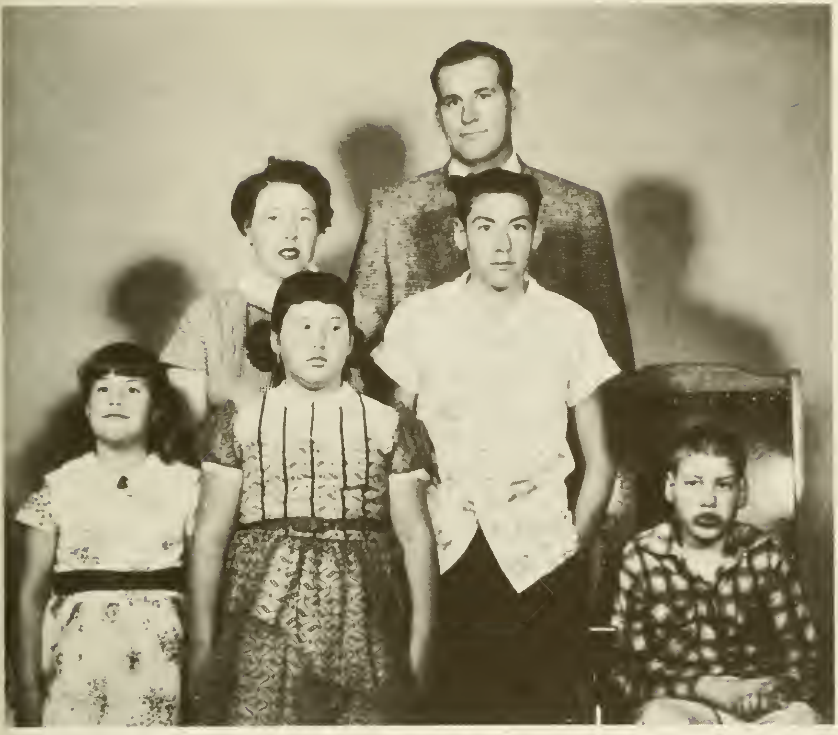
The screening of mentally retarded populations for PKU has been done for many years in a good number of institutions for the retarded,[7,8,9] whereas in many others such detection efforts are just starting.[25] Although it is unlikely that the intelligence of children picked up by this method can be improved very much by dietary control, diagnosing older children is such an important way of protecting subsequent siblings and other related infants with PKU that routine screening is strongly recommended in all institutions and schools or classes for the retarded, both public and private.

The success of such programs will depend on many cooperating organizations. Case finding will have to be followed systematically into the homes of the families in a way somewhat similar to screening families in which an active case of tuberculosis has been found.

A recent home survey of the siblings of 20 PKU patients at an institution of 3,000 population uncovered three previously undiagnosed cases.[26] Two of these were still young enough to receive benefit from treatment. On the basis of this experience, several recommendations have been made for followup work with families of PKU patients.

1. The families should be carefully oriented and counseled as soon as possible. The orientation should also include an explanatory letter or literature that describes the problem.

Figure 3.—Clinical Course in Untreated PKU.



The information should also be forwarded to the family physician. At least one information pamphlet for parents is now available.[27]

2. All siblings should be screened as soon as possible, even if the parents do not think they are retarded. Sometimes retardation in young children is unsuspected by the parents.
3. All newborn siblings should have serum phenylalanine determinations just prior to discharge from the newborn nurseries (at two or more days of age). If this is not possible, they should have urine tests at 2, 4, 6, 8 and 12 weeks of age. As an extra precaution, it is advisable to do similar followup urine tests, even on newborn siblings who have had a normal serum level.
4. The families should be encouraged to notify other relatives

so that young cousins, second cousins, nieces, and nephews can be tested for PKU during early infancy.

Well-baby populations

In most cases where PKU has been discovered in early infancy, the diagnosis had been made previously in a defective older sibling, as described above. If this were the only means by which young infants with PKU could be identified, it would mean the sacrifice of one child in each involved family.

A more recently instituted type of screening program involves routine screening tests on all infants.[4,5,6] This is the only way to find PKU children in previously unidentified families early enough for the infants to receive maximum benefit from treatment. It is suggested that the test be done at the first three well-baby checkups. Phenylpyruvic acid usually does not appear in the urine until the second or third week of life[22] and in some cases not until 6 weeks.[1] For this reason there is no value in testing the urine of babies in the newborn nursery.

At the present time many California health departments have joined in a routine screening program for PKU. The population area serviced by the participating health departments is in excess of three-fourths of California. The program would not be possible except for the full cooperation and enthusiasm of all of these health departments. The test being used, called the diaper test, will be described later in this book. As the program is long range, no final results can be reported at this time. However, it has already been proved that routine testing by this method is easily incorporated into the regular well-baby program, and the simplicity of the test has helped promote the enthusiastic support of the workers in the clinics. Also it has been proved that the test does uncover cases of PKU.[4] Already several PKU infants have been detected by routine screening programs both in the well-baby clinics and by private practitioners.

The health departments of several other States have incorporated this type of screening program into their well-child conference programs.

Shortly after the diaper test detection program was initiated in California, a routine screening program was started independently in England. There it is advised that all babies be tested at about 1 month of age during the first postnatal visit to the clinic or hospital. The screening test used is the Phenistix ® Test[28] as a urine or diaper test.[6] (See Testing Methods.) New cases are being discovered by routine screening in England.[6]

In Cincinnati, Ohio, a screening program has been started with the so-called filter-paper test.[5] (See Testing Methods.) In this program, each mother with a newborn infant receives instructions along with a piece of filter paper and a pre-addressed, stamped envelope. She is instructed that, when the infant is about 1 month old, the filter paper is to be placed in the baby's diaper until soaked with urine. It is then removed, dried by open-air contact, and sent via mail to a medical center. The first 10,000 such tests has resulted in the discovery of a young infant with PKU.

Other high risk groups

Because of the sometimes associated findings of behavior disturbances, convulsions, cerebral palsy and eczema in PKU patients, it may be advisable to screen children presenting such problems in clinics, centers, or in private practice, including those with or without mental retardation.

TESTING METHODS**

Several tests and modifications of tests are now available for the identification of PKU. A study was recently done at the College of Medical Evangelists School of Medicine, Los Angeles, Calif., to try to determine if there were any advantages or disadvantages of one test over another for screening purposes. In this study several thousand evaluations were made on 132 consecutive urine samples taken from 20 untreated institutionalized cases of PKU. The effects of many factors on the urine tests were measured, such as pH, specific gravity, turbidity, a.m. and p.m. voiding, age and sex of patients, hours of standing after voiding, et cetera.

The most important variable which affected all the tests was the freshness of the urine sample. Unless the urine has been frozen or a preservative added, it should be freshly voided for the best results (table I). Although deterioration is less rapid when the urine is dried on filter paper, 10 percent will no longer test positive after 3 days. Factors such as cost of the test and ease of administration were also compared. All the tests studied were comparable in accuracy, and each had enough specific merits to make that test valuable under certain circumstances (tables I and II).

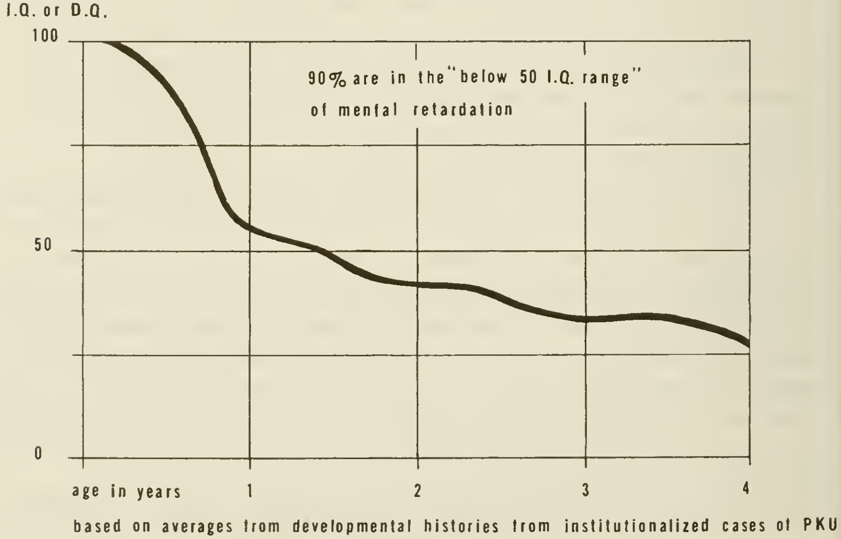
**This section is adapted from a paper in the November 1960 issue of the American Journal of Public Health [29] with the permission of the editor.

It was found that in each of these tests the value is dependent on some simple but specific precautions which if not understood and appreciated can easily cut the efficiency of that test considerably. Most of these pointers are included in the following discussion. On rare occasions PKU patients fail to excrete phenylpyruvic acid; therefore, the possibility of this disease can not be excluded on the basis of one negative urine test. Because the diagnosis is of great concern to the family and involves an expensive, long-term treatment, all positive urine tests should be confirmed with a serum phenylalanine level before the diagnosis of PKU is established and treatment begun. In a rare circumstance, when a serum phenylalanine level can not be obtained within a week, treatment may be started on the presumptive diagnosis of two confirmatory urine tests, i.e., ferric chloride and dinitrophenylhydrazine. In such a case, however, a sample of pretreatment serum should be frozen for later phenylalanine determination.

The test-tube test with ferric chloride

The test-tube test with ferric chloride is the oldest, best known, and most widely used of any of the diagnostic urine tests for PKU.[7, 8, 29] The color reaction of ferric chloride with phenylpyruvic acid is practically pathognomonic. Immediately there is a medium-dark, blue-green to gray-green color which fades in a matter of sec-

Figure 4.—Average Rate of Development for Untreated PKU Children.



onds, or minutes, depending upon the concentration of the phenylpyruvic acid in the urine and the strength of the ferric chloride solution being used. This fading of the color back to a neutral or negative urine color is most useful in differentiating the true phenylpyruvic acid reaction from most so-called false-positive reactions. Ingested salicylates, for example, will give the urine a blue-purple color upon application of ferric chloride. Unlike the phenylpyruvic acid reaction, however, this color does not fade away. Some of the color responses obtained when a ferric chloride solution is added to urine samples are: green from bile, homogentisic acid (alcaptonuria), the catecholamines (pheochromocytoma), and the urine of maple syrup urine disease,[30] red-brown from diacetic acid (acidosis), gray from melanin (malignant melanoma), light violet from chlorpromazine (Thorazine®) ingestion, and purple from proclorperazine (Compazine®) ingestion. Color reactions are fairly stable except with homogentisic acid. In this case the green color is extremely fleeting, disappearing within a second or two. The fact that the ferric chloride reagent will demonstrate the presence of various drugs and unusual metabolites other than phenylpyruvic acid does not impair the values of this test but rather makes it more interesting and more valuable.

The ferric chloride solution is very inexpensive and when made with distilled water and stored in polyethelene bottles it is stable indefinitely. We have preferred a 10 percent solution because of its quick, intense color reaction. When a few drops are added to a small amount (1 cc.) of urine, it has been found unnecessary to add acid first because the ferric chloride solution is itself very acid (pH 1.8).

The diaper test

The diaper test[4, 29] is a modification of the ferric chloride test-tube test. A drop of 10 percent ferric chloride is placed on a baby's wet diaper (or even if the diaper has dried since being wet), and a blue-green to gray-green color appears immediately. The concomitant use of a drop of acid is neither necessary nor desirable. As with the test-tube test, the color is transient. Many times a definitely positive test will fade in less than half a minute. Such fading starts in the center of the spot, and the last to fade is the green-rimmed periphery. Whether positive or negative, the spot on the diaper leaves a permanent stain. This is perhaps worth mentioning to the mother. Although thousands of infants have been tested, we have had no real complaints from the mothers.

The same false-positive reactions occur with the diaper test as with the test-tube test. The test has proved to be inexpensive and simple to perform. One penny's worth of solution can test several hundred infants. Of 104 PKU urine specimens allowed to stand at room temperature for 4 hours, 97 (or 93 percent) still definitely tested positive with ferric chloride (tables I and II).

In practice it was found that in considerable number of cases the infant did not have a wet diaper, and the mother had no wet diaper with her. For this reason, mothers are instructed to bring along with them on the initial and subsequent clinic visits the most recently wet diaper. In this way approximately 30 percent additional infants may be tested who would otherwise be missed.

The Phenistix® [28,29] test

Another modification of the ferric chloride test is the Phenistix® dip stick, a paper strip which is impregnated with a buffered ferric salt. This reagent, according to our studies, is second only to dinitrophenylhydrazine (DNPH) in sensitivity for phenylpyruvic acid. (See later discussion of the DNPH Test.) Of 104 PKU urines, 102 (or 98 percent) still definitely tested positive with Phenistix® after 4 hours of standing at room temperature (tables I and II). This test is excellent for routine screening of apparently well infants because the dip stick can be pressed against the still-wet diaper as well as dipped into a urine solution. These sticks are stable almost indefinitely if kept in their special container. False-positive reactions do occur with Phenistix® but less frequently than with ferric chloride. The color reaction of Phenistix® with phenylpyruvic acid is essentially the same as the ferric chloride test. The color also may fade away within a minute or so; thus, it would be impossible to place a Phenistix® in a baby's diaper and expect to come back later and get an accurate test result.

At present the Phenistix® costs approximately 8 cents a test; this is certainly inexpensive and should be no barrier to those physicians who wish to utilize it as a screening test in their practices. Phenistix® is slightly more cumbersome than the diaper-test for routine screening; on the other hand, it leaves no stain on the diaper.

The filter paper test [5,29]

The filter paper test is performed on ordinary white filter paper which has been wet with urine, dried, and then sent through the mail to the testing laboratory. The test is the same as the diaper test. The difference between the filter paper test and the diaper test is that the wet diaper which is tested is probably no more than several hours old, whereas the filter paper urine may be several days old before it is tested.

The question arises as to how long the dried, urine-soaked paper continues to give an accurate test. To evaluate this problem, 30 urines from known PKU patients were soaked on filter paper and dried to simulate the actual filter paper test. Inasmuch as the program as set up in Cincinnati involves experienced laboratory personnel, even the faintest trace of positive reaction was considered as positive. By the use of this criterion, the 30 specimens initially were all positive, but 2 of them were only very faintly positive. By 3 days, at room temperature, the average time one can expect between voiding and testing under such a program, 3 (10 percent) of the test specimens were negative. At 5 days, 5 (16.7 percent) were negative. By 1 week, 6 (20 percent) were negative. These results indicate that it would be a mistake to take one negative test as assurance that no PKU is present. If immediate testing of a filter paper sample sent through the mail is not possible, then store the sample in the freezer until ready to be tested. Freezing arrests or markedly retards the process of phenylpyruvic acid deterioration.

The cost of materials and supplies in this screening program is approximately 1 cent per test providing the parents supply their own stamps on the envelopes. The advantages and indications of such a program are: (1) the screening program can be initiated in practically all young infants (at least those who are born in hospitals); (2) this test might be advantageous for use on patients in out-of-the-way and distant places and perhaps for infants where there is no available wet diaper for testing at the office or clinic visit (table II).

The dinitrophenylhydrazine test-tube test

Properly prepared and used, the dinitrophenylhydrazine (DNPH) [29, 31] reagent is the most sensitive and reliable of the various urine tests for PKU. False-negative test reactions using DNPH on known untreated cases of PKU are rare (less than 1 percent). In our experience with over 100 consecutive urine samples, there were no false-negatives even after 18 hours of standing at room temperatures (tables I and II). Because other substances rarely found in urine will react to give a positive test with the DNPH, any positive test should be cross-checked with a ferric chloride test. Of the aforementioned substances which can give a color response with ferric chloride, only the diacetic acid and the urine of maple syrup urine disease give positive reactions with DNPH.

This reagent is prepared as follows: about 4 grams of 2–4 dinitrophenylhydrazine (an orange powder) are added to a liter of one normal hydrochloric acid. This mixture is heated in a hot water bath overnight to make a supersaturated approximately 0.3 percent solution of DNPH. The supernatant, clear-yellow solution is filtered off and stored in a dark glass bottle.

Table I.—Percentage of 104 PKU Urine Samples Giving Definitely Positive Reactions After Increasing Intervals of Exposure at Room Temperature*

Exposure time	Fe Cl$_3$ (test tube)	Fe Cl$_3$ (diaper test)	Dinitrophenylhydrazine	Phenistix
2 hours	99.1	94.2	100	99.1
4 hours	95.2	93.3	100	98.1
8 hours	95.2	91.3	100	98.1
12 hours	92.3	89.4	100	97.1
18 hours	90.4	84.6	100	96.2
24 hours	76.0	68.3	100	91.3

Table II.—Some General Comparisons of Five Current Testing Methods*

	Filter paper	Fe Cl$_3$ (test tube)	Fe Cl$_3$ (diaper)	Phenistix	DNPH
Ease of testing	+++	++	++++	+++	++
Ease of interpretation	+++	++++	+++	++++	+++
Low cost	++	+++	++++	++	+++
Sensitivity	++	+++	+++	++++	++++
Other path. detectable	+++	++	++	+	++

*Adapted from report to the Technical Committee on Clinic Programs for Mentally Retarded Children, Washington, D.C., Feb. 26–27, 1959.

The test is performed in the following manner: One-half to 1 cubic centimeter of urine is placed in a test tube. To this is added an equal amount of DNPH. *Immediately* after addition of the DNPH, the mixture is a clear, pale-yellow-orange solution, and it will remain this way if the test is negative. The test is positive when in the course of 1 to 5 minutes the solution gradually becomes an opaque, bright-yellow color. This is a permanent reaction and will be essentially unchanged if observed hours or even a day later. There is a possibility of some confusion in interpreting test results if the urine sample is initially cloudy. When the tester is in doubt, he should duplicate the test and compare the opacities of the older and fresher mixtures, and he should cross-check with a ferric chloride or Phenistix ® Test. The cost of chemicals for the DNPH solution is extremely small. By the use of 1 cc. of solution for each test, it is possible to make over 200 tests for 1 penny's worth of solution.

Serum phenylalanine determination

The main value and indication for the serum phenylalanine determination are for final confirmation of the diagnosis of PKU in cases seemingly positive by urine tests. No infant or child should be started on the long-term program of a low-phenylalanine diet without a blood sample being taken first. The serum specimen (2 cc.) can be safely stored in a freezer and tested later if an immediate serum phenylalanine determination is inconvenient or impossible. In this way there need be no long delay in initiating dietary treatment because of local lack of certain laboratory facilities.

Methods for determining serum phenylalanines[32,33,34,35] are too complex for description here. Many medical school centers and some research centers and commercial laboratories are set up to do these determinations (see Appendix A).

There are two other indications for the use of the serum phenylalanine level. Subsequent siblings born into a family where PKU is present in an older child have a 25 percent chance of also having PKU.[9, 10] Newborn infants with this disorder have normal cord blood phenylalanine levels; i.e., under 5 mg. per 100 ml. serum. By 2 or 3 days postnatally, however, the serum phenylalanine has risen to abnormally high levels (10 to 15 mg.), and a blood specimen at this time is adequate to make the diagnosis. However, it takes a week or longer (rarely up to 6 weeks) before the serum level is sufficiently high so that phenylpyruvic acid can be detected in the urine.[1,22] Thus it is suggested that blood specimens be taken on the newborn siblings of known cases of PKU just prior to their discharge home from the newborn nursery.[26] Babies in a newborn nursery are too young to be urine tested for PKU.

It might be advisable to determine the serum phenylalanine level on a child who seems to suggest strongly the diagnosis of PKU but whose urine tests are negative. There are instances of PKU in which serum phenylalanine levels, although definitely elevated above normal, were just at the renal threshold level so that spillage of metabolites into the urine was inconsistent.[36]

DIETARY TREATMENT

Dietary treatment for PKU was first described in the early 1950's[37,38,39] and has since been reported in enough cases to establish its efficacy in the treatment of infants and small children.[2,40,41,42] When the diet has been started in the first several months of life, mental deficiency has apparently been prevented. The rate and irreversibility of the deterioration are somewhat variable; however, it is generally felt that the diet might be tried on all children under 3 years of age and that many of these may be significantly improved. The cases of children above 3 years of age have to be considered individually. It is felt by some workers in this field that older PKU children who are only mildly retarded or who have marked behavioral or convulsive disorders are more likely to show benefit from diet management than others in the same age group.

The purpose of the diet is to lower the blood phenylalanine from the abnormally high levels caused by the disease (15–60 mg. per 100 ml. of serum) to near normal levels (1–3 mg.). Because all proteins in normally available foods are 4 to 6 percent phenylalanine, it is impossible to devise a diet from such foods that will lower the phenylalanine level and still provide sufficient protein for growth and repair. Therefore, all low phenylalanine diets are based on synthetic foods which provide amino acids with little phenylalanine. Most of these synthetic foods have been made with a modified casein hydrolysate. Several products have been available commercially in the United States [43,44] and Europe.[45,46] Actually, these special products are so low in phenylalanine that if given by themselves they would produce a phenylalanine deficiency, including poor growth and a paradoxical rise in serum phenylalanine due to catabolism of body protein. Phenylalanine is an essential amino acid and the body requires a certain minimal daily amount.[47,48,49] An opportunity is thus provided for varying the diet by the addition of low protein vegetables and fruits—with the goal of maintaining a serum level of from 2 to 6 mg. of phenylalanine per 100 ml. of serum. (These are believed to be safe levels. How high the phenylalanine can be kept and still get the best results has not been determined.) The serum level of phenylalanine at which phenylpyruvic acid will begin to appear in the urine is between 10 and 15 mg. per 100 ml.[39] Thus frequent urine tests are good as gross checks of dietary control, but they do not supplant the need of periodic serum level determinations. It is advised that these serum levels be obtained at intervals not less than every 2 to 4 months while a child is on the low phenylalanine diet (and more frequently during the early months of control). *The serum levels are necessary to detect both excesses and deficiencies of phenylalanine so the diet can be adjusted accordingly.*

Our experience to date has largely been with an American-made product, Lofenalac®.[44] Lofenalac® has fat, carbohydrate, and certain minerals and vitamins incorporated with the low phenylalanine casein hydrolysate. One measure (tablespoon) of Lofenalac® powder has approximately 1½ gm. of protein equivalent, with 7½ mg. of phenylalanine. One measure (tablespoon) added to 2 ounces of water makes a 20 calorie-to-the-ounce formula which has almost the same consistency, appearance, and components as milk minus 90 percent of its phenylalanine. It has a nut-like flavor which has been well accepted by almost all of our patients. Most of the children have taken it as a beverage either standard strength or somewhat concentrated. Several have preferred to take it mixed directly into their low protein food supplements. The powder can also be utilized in special low phenylalanine recipes for pastries, breads, puddings, ice creams, and sauces.[50,51] Realization on the part of the mother, or others responsible for feeding a child, of how the diet can be varied and still meet the child's needs will lead to easier control and success with the diet. Quite naturally it is easier to introduce this new diet to a small baby than to an older child.

In the early months of life, we supplement the baby's low phenylalanine formula with a small quantity of milk plus extra vitamins and iron. As the baby gets older, all varieties of fruits and certain low protein vegetables (i.e., carrots, beets, string beans, squash, turnips, tomatoes, etc.) are added. *These low protein foods continue to form the basis of the food supplements* and later, depending on the amount of phenylalanine allowed and the child's preference, two or three small servings of cereal, potato or cookies may be added to the daily menu. With all our patients on low-phenylalanine diets, we continue to give small doses of supplementary vitamins and iron as an extra precautionary measure. Actually with the exception of vitamin C the Lofenalac® Formula is probably adequate in these factors. Several sample diets for infants and young children are given in table III.

From the sample menus in table III, you will notice a handy rule of thumb. Children, about 1 year of age, need approximately 1 measure (tablespoon) of Lofenalac® per pound of body weight each day. For younger infants the need is proportionately greater, and for older children, it is proportionately less.[52] This plus the daily calorie and phenylalanine requirements is outlined more graphically in table IV.

One of the means of helping parents is to provide them the food lists and special recipes that have been devised for low-phenylalanine diets.[50,51] The food lists give the equivalent amounts of food that provide 15 mg. of phenylalanine, called one "equivalent" according to a plan devised by Lyman.[51] By substituting equivalents of various foods, the parents can easily vary the diet and still keep within the prescribed amount of phenylalanine. (See Appendix B for exchange lists for low-phenylalanine diet.)

We do not mean to suggest that every child will take to a low-phenylalanine diet without any difficulty. Depending on his personality, the older the child is, the more he will miss his previous diet, and the more resistance he will put up to the new diet. But in our

Table III.—Some Examples of Low Phenylalanine Menus

Age and weight	Formula	Breakfast	Midmorning	Dinner	Midafternoon	Supper	Bedtime
2 months (10 lbs.)	15 measures Lofenalac 2 oz. milk 26 oz. water	Five or six 5–6 ounce feeding of formula					
8 months (18 lbs.)	22 measures Lofenalac 2 oz. milk 25 oz. water	½ cup chopped peaches 8 oz. formula		½ cup chopped carrots 8 oz. formula		½ cup chopped pears 8 oz. formula	8 oz. formula
2 yrs. (26 lbs.)	26 measures Lofenalac 1 oz. milk 20 oz. water	½ cup dried rice cereal* with 3 oz. formula with sugar ⅓ cup orange sections 6 oz. formula		½ cup cooked carrots 2½ tbsp. mashed potato made with formula and 1 tsp. butter ½ cup apple sauce 6 oz. formula	2 animal cookies 6 oz. formula	3 tbsp. of green beans 3 pear halves 6 oz. formula	
4 yrs. (36 lbs.)	27 measures Lofenalac 25 oz. water	½ cup dried rice cereal* with 2–3 oz. formula 1 small orange 8 oz. formula	wedges of apple	½ cup cabbage and carrot salad with vinegar and oil dressing ½ cup homemade vegetable soup 1 peach half 8 oz. formula	3 animal cookies 4 oz. formula	½ banana ½ cup tapioca pudding made with pineapple juice 8 oz. formula	Synthetic fruit flavored drink

1 measure = 1 tablespoon
16 tablespoons = 1 cup
*Do not use any "protein fortified" cereals.

experience, the difficulties [53,54] that were encountered with older mixtures (i.e., diarrhea, starvation, severe weight loss, hypoglycemia, and convulsions) have not been a problem. Within a week even 2 and 3 year olds have been drinking the Lofenalac® and liking it—and without the use of special flavoring or sweetening. We agree with Umbarger [55] about the disadvantages of hospitalization. All of our children were started on the diet at home and none have required hospitalization because of the Lofenalac ® diet.

Public health nurses and nutritionists are valuable assistants in this field of diet management. However, we feel that any physician (not blessed with such helpers) who is able to spend some extra time with the family at the start can supervise this diet. Conscientious continued followup guidance and counseling are essential for long-range success of the program.

Table IV.—Some Basic Daily Requirements of the Low Phenylalanine Diet and Suggested Quantities of Lofenalac®

Age group	Total calories per pound of body weight	Total phenylalanine per pound of body weight (milligrams)	Measures of Lofenalac® per pound of body weight (tablespoons)
0–3 months	60–65	20–22	1¼–1½
3–12 months	55–60	18–20	1–1¼
1–3 years	50–55	16–18	¾–1
3–7 years	40–50	10–16	½–¾

The length of time that a child should be kept on the diet to obtain optimal and permanent benefit has been the subject of much interesting discussion. In the natural course of the disease, it seems that deterioration does not continue much beyond 3 years of age and this has been quoted as the age after which the special diet may not be necessary. The issue has been confused by the fact that a few PKU children who were not treated until after 3 years have shown good improvement. At the present time, scattered experiences are indicating that children over 3 are maintaining their I.Q.'s off the diet. However, since it seems to be true that the adverse personality effects of phenylketonuria as well as mental deficiency respond somewhat to the low-phenylalanine diet, it will be interesting to see whether this will be a factor in the duration of treatment. It will take a few more years to be certain of the long term effects of diet treatment on both mentality and personality.

The cost of these special dietary products is of practical interest. Manufacturers preparing these products as nonprofit service items are making every effort to supply them at as low a cost as possible. At present the dietary product can probably be provided to the parents through the pharmacy at from $0.75 to $2.00 a day, depending on the size of the child.

It should be realized that the child must be under a doctor's care at all times while on the diet to assure the maintenance of prescribed levels of phenylalanine both for maximal benefit to the child's mentality and to prevent dietary deficiency.

SUMMARY

It has been shown that the mental deficiency of phenylketonuria (PKU) can be prevented or favorably modified if a special low phenylalanine diet is started early in life. Those concerned with child health are faced with the challenge of finding these children during infancy. The history of the disease is reviewed briefly and the clinical picture and biochemical abnormalities are described. The various facets of the problem of case findings are discussed under screening of mentally retarded populations and screening of well babies. It is pointed out that the identification of the retarded child with PKU is of importance at any age because the family can then be alerted to the possibility of this condition in a younger sibling who could be treated. The screening of well babies is important as the only way of finding the first case in a family in time to prevent mental deficiency.

Tests used in diagnosing PKU are described and evaluated for the purpose of choosing the appropriate test and applying it with the most effectiveness.

Dietary treatment is described and general principles for prescribing the diet for various ages are outlined. It is suggested that all children under 3 years of age discovered to have PKU (and some selected children beyond this age) might be given a trial of treatment. It has not yet been established how long the special diet will be necessary. The actual upper limit for the serum phenylalanine level which will permit normal development is unknown, but it is suggested that the levels be kept within the range of 2 to 6 mg. per 100 ml. Examples of daily diets are included.

acknowledgments

We acknowledge the valuable assistance given to us by Mrs. Phyllis B. Acosta, M.S., Assistant Professor, College of Medical Evangelists School of Dietetics, Los Angeles, Calif., in preparing the section on Dietary Treatment and to Mrs. Ada W. Turner, B.A., Editor of Official Publications, College of Medical Evangelists, in giving manuscript suggestions. The illustrations used in this paper are adapted from a slide lecture on phenylketonuria in the Loan Library of Mead Johnson & Co.[56]

APPENDIX A

Some Laboratory Facilities Willing To Perform Serum Phenylalanine Determinations

As a way of providing some immediate assistance to persons having no local facilities available to perform serum phenylalanine determinations, several medical centers in the United States doing research in this field have been approached and have expressed a willingness to perform such determinations sent to them. The following names and addresses might be used for such purposes:

Armstrong, Marvin D., Ph. D.
The Fels Research Institute
Yellow Springs, Ohio

Berry, Helen K., M.A.
Guest, George M., M.D.
The Children's Hospital
Elland Avenue and Bethesda
Cincinnati 29, Ohio

Jervis, George A., M.D.
Letchworth Village
Thiells, Rockland Co.
New York

LaDu, Bert N., M.D.
Department of Health, Education, and Welfare
National Institutes of Health
Bethesda 14, Md.

Garrisi, Joseph A., M.D.
Department of Pediatrics
College of Medical Evangelists
1720 Brooklyn Avenue
Los Angeles 33, Calif.

Hsia, David Y., M.D.
Department of Pediatrics
The Children's Memorial Hospital
707 Fullerton Avenue
Chicago 14, Ill.

O'Brian, Donough, M.D.
Department of Pediatrics
University of Colorado Medical Center
4200 East Ninth Avenue
Denver 20, Colo.

This is admittedly an incomplete list of places able and willing to perform such services. As indicated, it is published here only as a way of suggesting a few resources which are willing to help until local resources are located or become available.

APPENDIX B

(Reprinted with permission from: Phenylketonuria: Dietary Management by Phyllis Brown Acosta and Willard R. Centerwall, in the Journal of the American Dietetic Association, Vol. 36, No. 3, March, 1960, p. 207.)

Exchange lists for low-phenylalanine diet

FOOD	AMOUNT
List I—Lofenalac 30 Mg. Phenylalanine—2 Equivalents*	
Lofenalac† (dry)	4 tbsp.
Lofenalac (reconstituted)	1 c.
List II—Vegetables 15 Mg. Phenylalanine—1 Equivalent	
Beans, green	
Strained and chopped	1½ tbsp.
Regular	3 tbsp.
Beets	
Strained	2 tbsp.
Regular	3 tbsp.
Cabbage, raw, shredded	4 tbsp.
Carrots	
Strained and chopped	3 tbsp.
Raw	¼ large
Canned	4 tbsp.
Celery, raw	1½ small stalks
Cucumber, raw	⅓ medium
Lettuce, head	2 leaves
Spinach, creamed—strained and chopped	1½ tbsp.
Squash	
Winter	
Strained	3 tbsp.
Chopped	6 tbsp.
Cooked	2 tbsp.
Summer, cooked	4 tbsp.
Tomato	
Raw	¼ small
Canned	2 tbsp.
Juice	2½ tbsp.
List III—Fruits 15 Mg. Phenylalanine—1 Equivalent	
Banana	4 tbsp.
Dates, dried	2
Fruit cocktail, canned	2½ tbsp.

Grapefruit	
Sections	⅓ c.
Juice	⅓ c.
Orange	
Sections	3 tbsp.
Juice	3 tbsp.
Grape juice	⅓ c.
Lemon juice	3 tbsp.
Peaches	
Raw	⅔ medium
Canned in sirup	1½ halves
Strained	5 tbsp.
Chopped	7 tbsp.
Pears	
Raw	⅓ medium
Canned in sirup	3 halves
Strained and chopped	10 tbsp.
Pears and pineapple, strained and chopped	7 tbsp.
Pineapple	
Raw	⅓ c.
Canned in sirup	1½ small slices
Juice	½ c.
Plums, canned in sirup	1½ medium
Plums with tapioca	
Strained	5 tbsp.
Chopped	7 tbsp.
Prunes	
Cooked	2 medium
Juice	⅓ c.
Strained	3 tbsp.
Raisins	1½ tbsp.
Strawberries	3 large
Tangerine	⅔ small
Watermelon	⅔ c.

List IV—Breads
30 Mg. Phenylalanine—2 Equivalents

Barley cereal, Gerber's, dry	2⅓ tbsp.
Biscuits‡	1 small
Cereal food, Gerber's, dry	2 tbsp.
Cookies, arrowroot	1½
Corn	2 tbsp.
Cornflakes	⅓ c.
Crackers	
Barnum animal	6
Saltines	3
Cream of Wheat, cooked	2 tbsp.
Farina, cooked	2½ tbsp.
Mixed cereal, Pablum, dry	1⅔ tbsp.
Oatmeal	
Gerber's strained	1⅔ tbsp.
Pablum, dry	1⅔ tbsp.
Potatoes, Irish	2½ tbsp.
Rice Flakes, Quaker	⅓ c.
Rice Krispies, Kellogg's	⅓ c.
Rice, Puffed, Quaker	½ c.
Sugar Crisps	¼ c.
Sweet potatoes or yams	
Cooked	3 tbsp.
Strained	4 tbsp.
Wafers, sugar, Nabisco	6
Wheat, Puffed, Quaker	⅓ c.

List V—Fats
5 Mg. Phenylalanine—1/3 Equivalent

Butter	1 tsp.
Cream, heavy	1 tsp.
Margarine	1 tbsp.
Mayonnaise	1½ tbsp.
Olives, ripe	1 large

List VI—Desserts
30 Mg. Phenylalanine—2 Equivalent

Cookies	
Rice flour	2
Corn starch	2
Ice cream‡	
Chocolate	⅓ c.
Pineapple	⅓ c.
Strawberry	⅓ c.
Vanilla	⅓ c.
Puddings‡	1 c.
Sauce, Hershey sirup	2 tbsp.

List VII—Free Foods; Little or No Phenylalanine; May Be Used as Desired

Candy	
Butterscotch	—
Cream mints	—
Fondant	—
Gum drops	—
Hard	—
Jelly beans	—
Lollipops	—
Cornstarch	—
Guava butter	—
Honey	—
Jams, jellies, and marmalades	—
Molasses	—
Oil	—

Sauces	
Lemon‡	—
White‡	—
Sirups	
Corn	—
Maple	—
Sugar	
Brown	—
White	—
Tapioca	—

List VIII—Foods to Avoid; High Phenylalanine Content; May Be Used Only Occasionally in Very Small Portions

Breads, most	—
Cheeses of all kinds	—
Eggs	—
Legumes, dried	—
Meat, poultry, fish	—
Milk	—
Nuts	—
Nut butters	—

---

‡Special recipe must be used.

Milk is high in phenylalanine (1 oz. contains 50 mg.), but it may be ordered in infants to keep phenylalanine blood levels up to normal.

*One equivalent may be defined as providing 15. mg. phenylalanine.

†Mead Johnson & Company.

APPENDIX C

Suggested Reading for General Review of Phenylketonuria

Jervis, G. A.: Phenylpyruvic Oligophrenia (Phenylketonuria), A. Res. Nerv. & Ment. Dis. Proc. 33: 259–282, 1954.

Wright, S. W., and Tarjan, G.: Phenylketonuria, A.M.A. J. Dis. Child. 93: 405–419 (April) 1957.

Knox, W. E., and Hsia, D. Y.: Pathogenetic Problems in Phenylketonuria, Am. J. Med. 22: 687–702 (May) 1957.

Lyman, F. L.: Phenylketonuria, New York J. Med. 58: 3653–3656 (Nov. 15) 1958.

Centerwall, W. R.: Phenylketonuria, A General Review, J.A.D.A. 36: 201–205 (March) 1960.

Literature for Lay Persons and Parents

Brecher, R., and Brecher, E.: The Conquest of Body Chemistry Diseases, Family Circle, October, 1957.

Centerwall, S. A., and Centerwall, W. R.: An Introduction to Your Child Who has Phenylketonuria, (7 pages), College of Medical Evangelists Press, Loma Linda, California, 1958.

Brecher, R., and Brecher, E.: Saving Children from Mental Retardation, The Saturday Evening Post, Nov. 31, 1959.

BIBLIOGRAPHY

1. Horner, F. A., and Streamer, C. W.: Effect of a Phenylalanine-Restricted Diet on Patients with Phenylketonuria; Clinical Observations in Three Cases. J.A.M.A., 161: 1628–1630. 1956.
2. Knox, W. E.: An Evaluation of Phenylketonuria with Diets Low in Phenylalanine. Pediatrics, 26: 1–11. 1960.
3. Centerwall, W. R., and Centerwall, S. A.: Phenylketonuria (Fölling's Disease): The Story of Its Discovery. J. Hist. Med. and Allied Sci. (In press).
4. Centerwall, W. R.: Phenylketonuria. J.A.M.A., 165: 392, 2219. 1957.
5. Berry, H. K., Sutherland, B. S., Guest, G. M., and Warkany, J.: Simple Method for Detection of Phenylketonuria. J.A.M.A., 167: 2189–2190. 1958.
6. Gibbs, N. K., and Woolf, L. I.: Tests for Phenylketonuria: Results of a One-Year Programme for Its Detection in Infancy and Among Mental Defectives. Brit. M. J., 2: 532–535. 1959.
7. Fölling, A.: Phenylpyruvic Acid as a Metabolic Anomaly in Connection with Imbecility. Nord. med. Tidskr., 8: 1054–1059. 1934.
8. Fölling, A.: Phenylpyruvic Acid as a Metabolic Anomaly in Connection with Imbecility. Ztschr. f. physiol. Chem., 227: 169–176. 1934.
9. Jervis, G. A.: Phenylpyruvic Oligophrenia: Introductory Study of 50 Cases of Mental Deficiency Associated with Excretion of Phenylpyruvic Acid. Arch. Neurol. & Psychiat., 38: 944–963. 1937.
10. Penrose, L. S.: Inheritance of Phenylpyruvic Amentia (Phenylketonuria). Lancet, 2: 192–194. 1935.
11. Armstrong, M. D., and Low, N. L.: Phenylketonuria. VIII. Relation Between Age, Serum Phenylalanine Level, and Phenylpyruvic Acid Excretion. Proc. Soc. Exper. Biol. & Med., 94: 142–146. 1957.
12. Cohen, P., and Kozinn, P. J.: Phenylpyruvic Oligophrenia in Jewish Child. J. Pediat., 34: 76–79. 1949.
13. Centerwall, W. R., and Neff, C. A.: Phenylketonuria: A Case Report of Children of Jewish Ancestry. Arch. Pediat. (In press).
14. Ferriera-Fernandes, J.: Phenylpyruvic Oligophrenia in Melanoderma; Preliminary Report. Brasil-med., 64: 225. 1950.
15. Stadler, H. E., Meyer, H., and Leland, H.: Phenylpyruvic Oligophrenia in a Mulatto; Possible Manifestation of the Pleiotropic Effect. J. Nerv. & Ment. Dis., 124: 205–207. 1956.
16. Hsia, D. Y., Driscoll, K. W., Troll, W., and Knox, W. E.: Detection by Phenylalanine Tolerance Tests of Heterozygous Carriers of Phenylketonuria. Nature, London, 178: 1239–1240. 1956.

17. Knox, W. E., and Messinger, E. C.: The Detection in the Heterozygote of the Metabolic Effect of the Recessive Gene for Phenylketonuria. Am. J. Human Genet., 10: 53–60. 1958.

18. Hsia, D. Y.: Phenylketonuria: The Phenylalanine-Tyrosine Ratio in the Detection of the Heterozygous Carrier. J. Ment. Defic. Res., 2: 8–16. 1958.

19. Jervis, G. A.: Phenylpyruvic Oligophrenia Deficiency of Phenylalanine-Oxidizing System. Proc. Soc. Exper. Biol. & Med., 82: 514–515. 1953.

20. Udenfriend, S., and Bessman, S. P.: The Hydroxylation of Phenylalanine and Antipyrene in Phenylpyruvic Oligophrenia. J. Biol. Chem., 203: 961–966. 1953.

21. Kaufman, S.: The Enzymic Conversion of Phenylalanine to Tyrosine. Biochem. et biophys. acta, 23: 445–446. 1957.

22. Armstrong, M. D., Centerwall, W. R., Horner, F. A., Low, N. L., and Weil, W. B.: The Development of Biochemical Abnormalities in Phenylketonuric Infants in Chemical Pathology of the Nervous System. New York: Pergamon Press. (In press).

23. Pare C. M., Sandler, M., and Stacey, R. S.: 5-Hydroxytryptamine Deficiency in Phenylketonuria. Lancet, 1: 551–553. 1957.

24. Paine, R. S.: The Variability in Manifestations of Untreated Patients with Phenylketonuria (Phenylpyruvic Aciduria). Pediatrics, 20: 290–302. 1957.

25. Allen, R.: Collaborative Research Pilot Survey of Known Cases of Phenylketonuria, Minutes, Technical Committee on Clinical Programs for Mentally Retarded Children. Children's Bureau, U.S. Department of Health, Education, and Welfare, Wash., D.C. (Feb. 26–27) 1959.

26. Centerwall, W. R., and Centerwall, S. A.: Phenylketonuria: Report of a Survey to Discover Treatable Siblings of Institutionalized Patients. Med. Arts and Sci., 13: 173–175. 1959.

27. Centerwall, S. A., and Centerwall, W. R.: An Introduction to Your Child Who Has Phenylketonuria, (7 pages). College of Medical Evangelists Press, Loma Linda, Calif. 1958.

28. Phenistix by Ames Company, Inc., Elkhart, Ind.

29. Centerwall, W. R., Chinnock, R. F., and Pusavat, A.: Phenylketonuria: Screening Programs and Testing Methods. A.J.P.H., 50: 1667–1677. 1960.

30. Menkes, J. H., Hurst, P. L., and Craig, J. M.: A New Syndrome: Progressive Familial Infantile Cerebral Dysfunction Associated with an Unusual Urinary Substance. Pediatrics, 14: 462–467. 1954.

31. Penrose, L. A., and Quastel, J. H.: Metabolic Studies on Phenylketonuria. Biochem. J., 31: 266–274. 1937.

32. Udenfriend, S., and Cooper, J. R.: Assay of L-Phenylalanine as Phenylethylamine after Enzymatic Decarboxylation; Application to Isotope Study. J. Biol. Chem., 203: 953–960. 1953.

33. Henry, R. J., Sobel, C., and Chiamori, N.: Method for Determination of Serum

Phenylalanine with Use of the Kapeller-Adler Reaction. A.M.A. J. Dis. Child., 94: 604–608. 1957.

34. Berry, H. K.: Paper Chromatographic Method for Estimation of Phenylalanine. Proc. Soc. Exper. Biol. & Med., 95: 71–73. 1957.

35. LaDu, B. N., and Michael, P. J.: An Enzymatic Spectrophotometric Method for the Determination of Phenylalanine in Blood. J. Lab. & Clin. Med., 55: 491–496. 1960.

36. Caudle, H.: personal correspondence.

37. Bickel, H., Gerrard, J., and Hickmans, E. M.: Influence of Phenylalanine Intake on Phenylketonuria. Lancet, 2: 812–813. 1953.

38. Woolf, L. I., Griffiths, R., and Moncrieff, A.: Treatment of Phenylketonuria with a Diet Low in Phenylalanine. Brit. M. J., 1: 57–64. 1955.

39. Armstrong, M. D., and Tyler, F. H.: Studies on Phenylketonuria. I. Restricted Phenylalanine Intake in Phenylketonuria. J. Clin. Invest., 34: 565–580. 1955.

40. Berendes, H., Anderson, J. A., Priggie, B., Ruttenberg, D., and Ziegler, M. R.: Phenylketonuria (Phenylpyruvic Oligophrenia). U. Minn. Med. Bull., 29: 498–511. 1958.

41. Clader, D. E.: Accelerated Intellectual Growth and Personality Development as Seen in Phenylketonuric Subjects During Medical Treatment. Am. J. Ment. Deficiency, 62: 538–542. 1957.

42. Centerwall, W. R., and Centerwall, S. A.: Early Diagnosis and Management of Phenylketonuria (Scientific Exhibit). A.M.A. Meeting, San Francisco. 1958.

43. Ketonil® by Merck Sharp & Dohme, Philadelphia, Pa., U.S.A.

44. Lofenalac® by Mead Johnson & Co., Evansville, Ind., U.S.A.

45. Cymogram® by Allen & Hanbury's Ltd., Bethnal Green, London, E.I., England.

46. Minafen® by Trufood Ltd., 113 Newington Causeway, London, S.E.I., England.

47. Rose, W. C., Leach, B. E., Coon M. J., and Lambert, G. F.: The Amino Acid Requirements of Man. IX. The Phenylalanine Requirement. J. Biol. Chem., 213: 913–922. 1955.

48. Snyderman, S. E., Pratt, E. L., Cheung, M. W., Norton, P., Holt, L. E., Jr., Hansen, A. E., and Panos, T. C.: The Phenylalanine Requirement of the Normal Infant. J. Nutrition, 56: 253–263. 1955.

49. Paine, R. S., and Hsia, D. Y.: The Dietary Phenylalanine Requirements and Tolerances of Phenylketonuric Patients. A.M.A. J. Dis. Child., 94: 224–230. 1957.

50. Acosta, P. B., and Centerwall, W. R.: Phenylketonuria, Dietary Management, Special Low-phenylalanine Recipes. J.A.D.A., 36: 206–211. 1960.

51. Lyman, F. L., and Lyman, J. K.: Dietary Management of Phenylketonuria With Lofenalac ®, Arch. of Ped., 77: 212–220. 1960.

52. Centerwall, W. R., Centerwall, S. A., Chinnock, R. F., and Acosta, P. B.: Phenylketonuria (PKU): Dietary Management of Infants and Young Children. J. Pediat. (In press).

53. Hsia, D. Y., Knox, W. E., Quinn, K. V., and Paine, R. S.: A One-Year Controlled Study of the Effect of Low-phenylalanine Diet on Phenylketonuria. Pediatrics, 21: 178–202. 1958.

54. Dodge, P. R., Mancall, E., Crawford, J. D., Knapp, J., and Paine, R. S.: Hypoglycemia Complicating Treatment of Phenylketonuria with a Phenylalanine Deficient Diet: Report of Two Cases. N.E.J.Med., 260: 1104–1111. 1959.

55. Umbarger, B.: Phenylketonuria: Treating the Disease and Feeding the Child. A.M.A. J. Dis. Child., 100: 908–913. 1960.

56. Centerwall, W. R. and Lyman, F. L.: Phenylketonuria, A Slide Lecture General Review. Loan Library, Mead Johnson & Co., Evansville, Ind. 1960.

U. S. GOVERNMENT PRINTING OFFICE : 1961 O - 579423

For sale by the Superintendent of Documents, U.S. Government Printing Office
Washington 25, D.C. — Price 15 cents.

BOSTON PUBLIC LIBRARY
3 9999 05708 7023

children's bureau publication 388—1961

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE

Social Security Administration
Children's Bureau